

Drug and Substance Abuse in Refractory Epilepsy

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ABSTRACT

Drugs and substances abuse in patients with refractor epilepsy were investigated in this study which includes 924 patients with intractable epilepsy were studied for serum levels of antiepileptic drugs and for drugs and substances abuse. Positive results for abuse were detected in 246 patients (26.62%), 56.5% of them were in the age group 20 – 30 years. Males outnumbered females with a sex ratio 1.46 : 1. Cannabis was the first abused drug as it was detected in 29.27% followed by opiates in 21.95%, alcohol in 17.88%, benzodiazepine in 16.26%, tricyclic in 8.54%, barbiturates in 6.1%. So, a screening test for drugs and substances abuse must be done in cases with resistant epilepsy even if patients deny the use of them. (Egypt J. Neurol. Psychiat. Neurosurg., 2008, 45(2): 387-394)

INTRODUCTION

Seizures often occur in substance abusers. The mechanism may be indirect as a result of infection (particularly cerebral complications of endocarditis or AIDS in parenteral drug users), trauma (as a consequence of intoxication or of violence associated with drug use), stroke (hemorrhagic or ischemic), and metabolic derangement (including hyponatremia, hypocalcemia, renal failure and, particularly in alcoholics, hypoglycemia). Depending on the agent, direct mechanisms can be either intoxication or withdrawal in subjects physically dependent on a drug^{1,2}.

Due to the ever-increasing problem of drug abuse among young people and adolescents, the involvement of a drug should be suspected whenever there is a temporal relationship between the use of the drug and the onset of a neurological syndrome and when the other known risk factors have been excluded³. However, since addicts often use mixtures of drugs and do not give an honest report of their usage, it is difficult to assess the role of an individual drug⁴.

The aim of the present work is to study the etiology of non-response to antiepileptic drugs by estimating their serum levels and screening of drugs

and substance abuse in patients with resistant epilepsy.

MATERIALS AND METHODS

This study was conducted in epilepsy out patient clinic, Neurology Department, Mansoura University Hospital, between January 2005 and December 2007.

After exclusion of those with symptomatic epilepsy or non compliance to treatment or with epilepsy other than generalized tonic-clonic seizures, 924 patients with resistant epilepsy were included.

They were subjected to:

- Toxicology screen for detection of drug and substance abuse by analysis of urine and blood samples.
- Measurements of the level of antiepileptic drugs in the blood (carbamazepine, valproic acid, phenytoin).

These were done by EMIT (Enzyme Multiplied Immunoassay Test) system.

Instrument:

Syva Solaris System, an automated drug analyzer designed to work with the Syva Emit assay

tests. The cut off concentration of abused drugs and substances tested was opiates (300 ng/ml), barbiturates (200 ng/ml), benzodiazepines (200 ng/ml) and cannabinoids (50 ng/ml), tricyclic antidepressants (300 ng/ml) and alcohol (positive or negative at any concentration). All assays run on the system use of homogenous immunoassay technique.

RESULTS

Positive results for drug and substance abuse were found in 246 of 924 patients (26.62%).

The age of patients ranged between 10 – 50y with a mean age 23.74 ± 6.51 years. 56.5% of them were in the age group 20 – 30 years, followed by those aged 30 – 40 years (26.02%). Adolescents (10 – 20) years accounted for 10.98% of the patients. As regards sex, the present study revealed that males outnumbered females (59.35% and 40.65% respectively) with a sex ratio 1.46 : 1 (Table 1).

Cannabis was the first abused drug (29.27%), opiates was the second drug abused by patients (21.95%) followed by alcohol (17.88%), benzodiazepine (16.26%) tricyclic antidepressants (8.54%) and finally barbiturate constituted (6.1%) (Table 2).

The study showed that in males the most common abused substance was cannabis (33.56%) followed by alcohol (30.14%) then opiates (21.23%) and benzodiazepines (6.85%), both tricyclic and barbiturates (4.1%), while the most of females were likely to abuse benzodiazepines (30%), the remaining abused; cannabis (23%), opiates (23%), tricyclic (15%) and barbiturates (9%) (Table 3).

Table (4) showed the levels of carbamazepine, valproate and phenytoin assays for 115, 76 and 55 patients respectively. Only 17 patients show serum level of antiepileptic drugs within therapeutic range, but 169 patients levels were below it and 60 patients with levels above it.

Table 1. Demographic data of patients with drug and substance abuse.

Age group	Male		Female		Total	
	No	%	No	%	No	%
10 – 20	17	11.64	10	10	27	10.98
20 – 30	83	56.8	56	56	139	56.50
30 – 40	36	24.66	28	28	64	26.02
40 – 50	10	6.85	6	6	16	6.51
Total	146	100.0	100	100.0	246	100.0

Table 2. Type of drug and substance abuse in difference age group.

Type of drug abuse overdose	Age group								Total	
	10 – 20		20 – 30		30 – 40		40 – 50			
	No	%	No	%	No	%	No	%	No	%
Cannabis	10	37.04	32	28.1	19	27.2	11	31.4	72	29.27
Opiates	7	25.92	25	21.9	14	20	8	22.9	54	21.95
Alcohol	3	11.11	21	18.4	13	18.6	7	20	44	17.88
Benzodiazepines	3	11.11	18	15.8	14	20	5	14.3	40	16.26
Tricyclic	2	7.41	10	8.8	5	7.1	4	11.4	21	8.54
Barbiturates	2	7.41	8	7	5	7.1	-	-	15	6.1
Total	27	100	114	100	70	100	35	100	246	100

Table 3. Patients (n=246) with drug abuse and seizures by type of drug abuse and sex.

Type of drug abuse overdose	Males		Females		Total	
	No	%	No	%	No	%
Cannabis	49	33.56	23	23	72	29.27
Opiates	31	21.23	23	23	54	21.95
Alcohol	44	30.14	-	-	44	17.88
Benzodiazepines	10	6.85	30	30	40	16.26
Tricyclic	6	4.1	15	15	21	8.54
Barbiturates	6	4.1	9	9	15	6.1
Total	146	100	100	100	246	100

Table 4. Results of antiepileptic drugs assay (n=246) by EMIT system.

Sex	Male				Female				Total
	Under Assay	Within Therapeutic Range	Over Assay	Total	Under Assay	Within Therapeutic Range	Over Assay	Total	
Carbamazepine	59	5	13	77	30	3	5	38	115
Valproic	23	1	10	34	15	7	20	42	76
Phenytoin	30	-	5	35	12	1	7	20	55
Total	112	6	28	146	57	11	32	100	246

DISCUSSION

Recreational drug abusers are at increased risk for seizures by a variety of mechanisms^{1,2}. Seizures precipitated by recreational drug abuse are usually caused by acute intoxication in contrast to the withdrawal seizures encountered in subjects with alcohol abuse³.

Drug abusers are prone to serious traumatic injuries⁵ and are frequently affected by infectious diseases, particularly AIDS⁶.

On the contrary, some reported that seizures are moderately infrequent complication of illicit drug use. In a prospective study, Alldredge et al.⁷ reported recreational drug-induced seizures in 47 patients among 186 000 inpatient admissions (0.025%) over a 12-year period.

The process of addiction, after repeated administration of drugs involves alterations in the function of neurons, their transmitters and ultimately the neural circuits³.

In this work toxicology screening for substance and drug abuse was done for 924 patients with resistant epilepsy (after exclusion those with organic brain lesion and who were not compliant to antiepileptic treatment). Positive results were obtained in 246 patients (26.62%).

The males outnumbered females (59.35% & 40.65% respectively) with a sex ratio of 1.46 : 1.

The problem of drug abuse is increasing among young people and adolescence³. This study revealed that the highest age group of abuse was between 20 – 30 years (56.5%) followed by the age group 30 – 40 years (26.02%). Teenagers represent 10.98%.

The risk of seizures increased in elderly people, probably owing to age-related reduction in metabolism and clearance that leads to drug accumulation, despite dosages well tolerated in younger patients⁸. Olson et al.⁹ reported that seizures in elderly patients were more likely to result in complication and death.

In the current study, it has been found that in males, abuse of cannabis was 33.56%, followed by alcohol 30.1%. In females benzodiazepines was the commonest (30%) followed by cannabis and opiates (23% for each).

As regards type of seizure, our all patients suffered from generalized tonic-clonic seizures; however, focal and generalized seizures as well as status epilepticus have been described, but the seizures are usually of the generalized tonic-clonic variety and may follow ingestion, snorting, smoking or injection of a drug. It is important to note that the seizure problems related to recreational drug use are usually caused by acute intoxication, in contrast to the withdrawal seizures encountered in subjects who have been abusing alcohol, benzodiazepines or barbiturates. The pathophysiologic mechanism underlying seizures triggered during acute drug intoxication is unclear, but brain oedema has been suggested. Seizures frequently precede fatal intoxication, which implies that the patient should be treated immediately in an intensive care unit³.

Marijuana use or withdrawal could potentially trigger seizures in susceptible patients¹⁰. In this study, cannabis was the most common abused drug in 29.27% of patients (49 males, 23 females), 32 of them in the age group 20 – 30 years. The mechanism by which marijuana affects seizures is not well defined. Dantas¹¹ reported that in the general population the increased use of marijuana is influenced by gender (male), youth and unemployment. The relation between marijuana (cannabis sativa) and epilepsy is still controversial. In addition to reports supporting its anticonvulsant effects, a few reports support proconvulsant properties of marijuana, which may be related to withdrawal hyperexcitability^{10,12,13}. This is very important issue because of ethical aspect as some of the components of cannabis have psychotropic effects¹¹. Further study is needed to clarify these effects. Experimental data, however, show that its principal psychoactive agent, Δ^9 -tetrahydrocannabinol, has serotonin-mediated anticonvulsant properties¹⁴.

Another cannabinoid compound, cannabidiol, appears to be anticonvulsant in both animals and humans².

In the present study, 54 patients (21.95%) were opiate abusers (31 males and 23 females), they were mostly in the age group 20 – 30 years. Although opioid agonists lower seizure threshold in some

animal models, seizures are an unusual feature of heroin or morphine overdose; their occurrence requires a search for another cause¹⁵. Except for neonatal withdrawal in cases of dependence developed in utero, seizures are not a feature of opiate withdrawal. Most cases of seizures in opioid abuse, whether occurring acutely or during withdrawal, are probably due to secondary causes, including repeated self-injections with unsterile or embolic material or the use of additional agents such as cocaine or ethanol¹⁶.

Also, Saboory et al.¹⁷ reported that high-dose opioid therapy can precipitate seizures; however, the mechanism of such a dangerous adverse effect remains poorly understood. However, they suggested that the pro-seizure effect of morphine is mediated through selective stimulation of mu and kappa opiate receptors but not the activation of the delta receptor system.

Alcohol dependence is a widespread psychiatric disorder, affecting 5.4% of the general population lifetime¹⁸.

This study revealed that 44 patients (17.88%) abused alcohol, all were males. In a case-control study of 308 patients with seizures and 294 controls at Harlem Hospital in New York City, it was concluded that the total daily dose of ethanol, rather than the abrupt cessation of intake, was the principle risk factor for seizures. These investigators failed to demonstrate a clear-cut temporal relationship between seizures and early abstinence, with many seizures occurring during active drinking or more than a week after stopping. So the authors proposed that alcohol is proconvulsant acutely as well as in its withdrawal¹⁹.

The most serious risk of seizures in connection with alcohol use is withdrawal. Alcohol withdrawal lowers the seizures threshold, an effect that may be related to alcohol dose, rapidity withdrawal and chronicity of exposure¹⁰.

Ethanol can also precipitate seizures in known epileptics, but the amount required is disputed²⁰. Seizures usually occur in those who have abused alcohol for at least 10 years, and some studies found the risk of seizures to increase with repeated bouts of withdrawal, suggesting a kindling phenomenon²¹.

It is important to recognize that alcohol predisposes to many medical and metabolic conditions that can mimic or cause seizures.

Hyponatremia and hypoglycemia associated with alcoholism can cause seizures²².

The pathophysiology of ethanol-related seizure has not been fully elucidated. Ethanol acts at many levels of the neuroaxis, especially complex polysynaptic systems such as the reticular formation and parietal association cortex. It indirectly affects a number of neurotransmitter systems, especially glutamate and γ -aminobutyric acid (GABA), but also norepinephrine, dopamine, serotonin, acetylcholine, and adenosine. Ethanol binds to glutamate and GABA receptors, blocking glutaminergic neurotransmission and facilitating GABAergic neurotransmission. Up-regulation of glutamate receptors and down-regulation of GABA receptors then occurs; and when ethanol is removed, the result is an excitotoxic state, possibly accounting for seizures and delirium tremens. Repeated exposure might cause more lasting neuronal damage, accounting for seizures independent of withdrawal²³.

Perez-Velazquez et al.²⁴ reported a significant increase in the high voltage activated calcium currents during the withdrawal period in the withdrawal seizure prone mouse strain, they suggested that an increase in calcium currents is one factor involved in the alcohol withdrawal hyperexcitability.

In our study, 40 patients (16.26%) abused benzodiazepine and 15 patients (6.1%) abused barbiturates. Benzodiazepines per se are relatively atoxic substances. In the central nervous system benzodiazepines bind to benzodiazepine receptors, which belong to the GABA-A receptor complex. This receptor is the most abundant inhibitory receptor in the mammalian brain²⁵.

Most of the benzodiazepines relieve anxiety and act as muscle relaxants. However, potentially life-threatening seizures may occur following the withdrawal of benzodiazepines and barbiturates. Drug addicts sometimes try to ameliorate their withdrawal symptoms or attenuate the side-effects of psychostimulants with benzodiazepines. Furthermore, drug abusers may also try to enhance the effect of other abused drugs by self-administering benzodiazepines³.

Benzodiazepine withdrawal after long-term use is, at least in some cases, related to epileptic seizures. These fits are usually grand mal seizures²⁶. The peak liability to seizures occurs between 5 and 7

days after discontinuation of long-acting benzodiazepines and between 2 and 4 days after discontinuation of barbiturates, depending on the pharmacokinetic properties of the abused drug²⁷. The pathophysiologic mechanisms underlying the transiently lowered seizure threshold shortly after the discontinuation of benzodiazepine and barbiturate abuse have been ascribed to several bio-organic changes in the brain. These include effects of the drugs on both the GABA and glutamate receptor-mediated functions. In experimental animals, both diazepam and pentobarbital withdrawal syndromes seem to be partially genetically determined²⁸.

Because depression is common in the general population and occurs even more often in patients with epilepsy (up to 50%), and because treatment of depression usually requires long-term drug treatment, the choice of antidepressant medication must be made carefully, taking into account the possible effect on seizure threshold²⁹.

The occurrence of seizures was reported with cyclic antidepressants either by deliberate administration⁽³⁰⁾ or by poisoning^{9,31}.

In this study, tricyclic antidepressants were detected in 15% of female and 4.1% of males and was common in age group 20 – 30 years.

Olson et al.⁹ found that cyclic antidepressants poisoning was found in 29% of 191 cases of seizures with drug intoxication and reported that the seizures with cyclic antidepressants was more likely to be associated with death. Dailey and Naritoku³² concluded that it is the antihistaminic, antimuscarinic, and local anaesthetic properties of antidepressants that are most likely responsible for any increased susceptibility to seizures. Even simple side effects of medication, however, such as drowsiness, can lower the seizure threshold in susceptible patients.

As regard the increased seizure risk with antidepressant, the highest risk of seizures has been reported with the heterocyclic antidepressant, the dopamine- or norepinephrine-specific reuptake inhibitor bupropion and the quaternary antidepressant maprotiline. The tricyclic antidepressants (TCAs) have the next highest seizure risk (which is increased by toxic levels). The newer selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, fluvoxamine, citalopram, and paroxetine) and

serotonin receptor modulators (trazodone and nefazodone) are intermediate in risk, as is venlafaxine, a combined norepinephrine and serotonin reuptake inhibitor. The monoamine oxidase inhibitors (MAOIs) carry the least risk³³.

The risk of seizures in patients taking antidepressant drugs depends on three factors³²⁻³⁵. The intrinsic epileptogenic or antiepileptic potential of the antidepressant; the amount of active drug that enters the brain, which depends on the dose, pharmacokinetics, and transport across the blood-brain barrier, the patient's seizure threshold, which depends on genetic factors, remote brain injury, previous febrile or acute symptomatic seizures, and use of alcohol or other substances.

The complex neurotransmitter effects of antidepressant drugs make it impossible to offer simplistic assumptions about their proconvulsant effects. Recent experimental studies of AEDs used to treat depression lead to the conclusion that it is unlikely that alterations in serotonin and norepinephrine levels are related to an increased risk of seizures³². In fact, some studies suggested that fluoxetine³⁶ and doxepine³³ may occasionally have anticonvulsant properties.

Substance abuse may be the cause of resistant epilepsy as they are epileptogenic by themselves or due to drug-drug interaction with the antiepileptics. The study of serum antiepileptic levels in our patients showed that they were within therapeutic range only in 17 patients and were below in 169 patients and above in 60 patients.

Birkett et al.³⁷ reported a 49-year-old female with chronic alcoholism and epilepsy, treated with phenytoin, began to convulse when treatment with disulfiram (an inhibitor of phenytoin metabolism) was discontinued. The patient at this stage was resistant to the large doses of phenytoin, apparently owing to induction of the metabolism of this drug by chronic alcohol intake.

Reference to drug interaction charts is necessary to anticipate the effects of one drug on another, as there are several isoenzymes of both the CYP450 and GT systems. In general, antidepressant and antipsychotic drugs are metabolized by CYP2D6 and CYP1A2, the enzyme systems that also metabolize carbamazepine. Most benzodiazepines and newer antipsychotic agents, as well as most other AEDs except phenytoin, use CYP3A4.

Phenytoin and a few benzodiazepines use CYP2C9. Valproic acid is also metabolized by the glucuronyl transferase system of enzymes, as are the tricyclic drugs^{33, 36}.

When an AED is added to an antidepressant, induction of hepatic enzymes may decrease the antidepressant's effectiveness³⁸. Sedating antidepressants may trigger seizures in patients whose seizure threshold is lowered by drowsiness³².

Enzyme-inhibiting antidepressant drugs, such as the SSRIs and TCAs, may require downward adjustment in the dosage of concurrently administered AEDs that are also metabolized by the cytochrome P-450 (CYP450) microsomal system in the liver. In other cases, phenytoin and carbamazepine inhibit the metabolism of antidepressant drugs, like fluoxetine or the TCAs, which leads to unintended toxicity from the antidepressant^{33, 36}.

Recommendations:

A screening test for drug and substance abuse is performed if drug abuse or withdrawal is suspected in patients with resistant epilepsy even if patient denies the use of them.

To confirm the results of EMIT, further study is needed by using GCMS (gas chromatography mass spectrum) as it is more sensitive and more specific than EMIT system.

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الملخص العربى

الإدمان فى الصرع الغير مستجيب للعلاج

استهدفت هذه الدراسة البحث عن الإدمان فى مرضى الصرع الغير مستجيبين فى العلاج الدوائى. تمت الدراسة على 924 مريضاً بنوبات صرعية كبرى غير مستجيبين للعلاج الدوائى وقد أجرى لهم قياس بعض مواد الإدمان فى الدم مع قياس بعض الأدوية ومواد الإدمان مع قياس مستوى الأدوية المضادة للصرع فى مصل الدم. وقد ظهرت نتيجة إيجابية فى 246 مريضاً (26.62%) ، وكانت نسبة الذكور إلى الإناث 1.46 : 1. وظهرت أعلى نسبة فى الفئة العمرية من 20 – 30 عام ، وقد ظهر أن مادة القنب (الحشيش) موجودة بنسبة 29.27% ومادة الأفيون بنسبة 21.95% والكحول بنسبة 17.88% والبنزوديازيبين بنسبة 16.26% ومواد مضادة للاكتئاب بنسبة 8.54% والبريتيورات بنسبة 6.1%.

ولذلك ننصح بعمل تحليل لهذه المواد فى أى مريض مصاب بنوبات صرعية غير مستجيبة للعلاج الدوائى.